CLIN Professional 2001-10-24 17:23:15 EDT N Engl J Med 2001;345:1223-1229. MESH D006757 Hospital Units implicit MESH D002053 **Burn** Units SNOMED-RT-0203 DD-0010D Injury of integument implicit SNOMED-RT-0203 DF-00000 Disease, NOS implicit SNOMED-RT-0203 DD-52024 **Burn** any degree involving 40-49 percent of body surface SNOMED-RT-0203 C-80110 Antiarrhythmic drug, NOS implicit SNOMED-RT-0203 DD-52025 **Burn** any degree involving 50-59 percent of body surface SNOMED-RT-0203 C-80116 Class II antiarrhythmic drug, NOS implicit SNOMED-RT-0203 F-01001 Finding, conclusion AND/OR assessment implicit SNOMED-RT-0203 C-80000 Cardiovascular drug, NOS implicit SNOMED-RT-0203 F-01003 Finding by function implicit SNOMED-RT-0203 D0-00050 Skin lesion, NOS implicit MESH D006268 Health Facilities implicit SNOMED-RT-0203 C-80130 Cardiac adrenergic blocking agent, NOS implicit SNOMED-RT-0203 DD-52026 **Burn** any degree involving 60-69 percent of body surface SNOMED-RT-0203 C-80135 beta-Blocking agent, NOS implicit SNOMED-RT-0203 C-80136 Non-selective beta-blocking agent, NOS implicit SNOMED-RT-0203 DF-00800 Disease by body site implicit SNOMED-RT-0203 C-50000 Drug, NOS implicit MESH D015278 Intensive Care Units, Pediatric MESH V000020 MeSH implicit SNOMED-RT-0203 F-60000 General metabolic function, NOS implicit SNOMED-RT-0203 C-500F1 Generic drug, hormone, vitamin AND/OR blood product implicit SNOMED-RT-0203 F-60003 Hypermetabolism SNOMED-RT-0203 DD-00001 Injury (disorder) implicit SNOMED-RT-0203 G-3000 SNOMED RT Concept implicit MESH D007362 Intensive Care Units SNOMED-RT-0203 DD-52000 **Burn** (disorder) implicit SNOMED-RT-0203 D0-00000 Disease of skin and subcutaneous tissue, NOS implicit SNOMED-RT-0203 D0-00099 Disorder of integument implicit SNOMED-RT-0203 F-61002 Substance implicit SNOMED-RT-0203 C-80450 **Propranolol** SNOMED-RT-0203 F-60020 **Catabolism** MESH U000008 Health Care (MeSH Category) implicit MESH D005159 Health Care Facilities, Manpower, and Services implicit SNOMED-RT-0203 D0-00004 Disease of skin, NOS implicit SNOMED-RT-0203 F-00000 Biological function, NOS implicit SNOMED-RT-0203 F-600F1 Metabolic system finding implicit SNOMED-RT-0203 DD-000F7 Injury of anatomical site implicit SNOMED-RT-0203 F-08100 Childhood

Clinical

Propranolol reduces catabolism due to severe burns in children

Last Updated: 2001-10-24 17:23:15 EDT (Reuters Health)

By Karla Gale

WESTPORT, CT (Reuters Health) - In children with burns over 40% of their body surface area,

beta-blockade with **propranolol** decreases resting energy expenditure and muscle **catabolism**, according to a report in The New England Journal of Medicine for October 25.

"The catabolic state persists for up to a year after the time of injury, and children of this age may even stop growing," Dr. David N. Herndon pointed out in an interview with Reuters Health. "Reversal of the catabolic response during acute hospitalization can allow them to grow normally, be stronger and return to regular activities more quickly."

Dr. Herndon and associates, of Shriners Hospitals for Children at the University of Texas, in Galveston, randomly assigned 13 children to oral **propranolol** for at least 2 weeks, while 12 children were relegated to normal treatment.

Following the second surgery for autografting, **propranolol** was started at 0.33 mg/kg every 4 hours. The dose was adjusted until the patient's heart rate was decreased 20% from baseline, to a final average dose of 1.05 mg/kg every 4 hours.

In the control group, resting energy expenditure increased by a mean of 140 kcal/day and oxygen consumption by 25 mL/min between baseline and 2 weeks. In contrast, patients in the **propranolol** group had significant decreases, by 422 kcal/day and 56 mL/minute, respectively ($p = 0.001$ and 0.002).

Over the same period of time, control patients lost about 9% of their fat-free mass, compared with a loss of about 1% in the **propranolol** group ($p = 0.003$).

Dr. Herndon also recommends **propranolol** for use in patients under other types of physiologic stress, such as those who have experienced a long bone fracture, septicemia, or treatment in an intensive care unit.

"The key to using it safely is to decrease the heart rate towards normal," he noted, "but to monitor the heart rate so as not to overshoot. You don't want the patient to become hypotensive."

He stressed that **propranolol** should not be used in asthmatics or in people subject to bronchospasm. Under those circumstances, metoprolol, which does not activate asthma, would be a more appropriate agent, he said.

In future research, Dr. Herndon's team plans to test the results of beginning **propranolol** treatment earlier after injury and for more extended periods.

Dr. Robert L. Sheridan, of Shriners Burns Hospital in Boston, notes in an editorial that children with serious inhalation injury and children requiring mechanical ventilation were not included in the study, so "the use of **propranolol** in such children should therefore be considered separately."

He also recommends that **propranolol** "should be used cautiously and only in an intensive care unit."

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Protein and energy requirements following burn injury

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Abstract

The response to severe burn injury requires conscientious nutritional support. This should be provided by the enteral route whenever clinically possible. Onset of nutritional support should not begin until the shock response is adequately resuscitated and the patient is clinically stable. Patients should be kept in a warm environment with occlusive dressings over the wounds to minimize heat loss, thereby reducing caloric requirements. Optimal caloric intake is best determined by measurements of resting energy expenditure (REE) in the fed state and multiplying that value by 1.2 to account for the small amount of activity. If direct measurement of REE is not possible, then the basal energy expenditure as predicted by Harris and Benedict can be multiplied by 1.5 to get an average value for caloric requirement. This level of intake should be modified according to the individual response. At least 50% of non-protein calories should be carbohydrate

and 20% fat; the source of the remainder of the calories is probably not important. Protein intake should be about 1.5 g protein/kg/d in adults, but may be as high as 2.0 or even 2.5 g protein/kg/d in small children.

1. Introduction

Injuries as severe as a third degree **burn** over 10% of the body surface have minimal effect on metabolic regulation or food intake. Consequently, whereas such injuries may be extremely painful and require skilled medical care for optimal recovery, they do not present a significant nutritional problem. On the other hand, severe **burn** injury over 30% of the body surface or more results in a pronounced metabolic response that has prolonged nutritional implications. The understanding of the nature of this response and the consequent changes in nutritional requirements is important not only for the optimal treatment of such patients, but also because many aspects of the response to **burn** injury can serve as a more general model of the so-called 'stress response'. This is because the extent of injury is quantifiable and the state of critical illness is maintained for a long enough time (often weeks) to enable nutritional and metabolic studies.

2. Resting energy expenditure

2.1. Mechanism of hypermetabolism

Resting energy expenditure (REE) after **burn** injury can be as much as 100% above that predicted from standard tables for size, age, sex and weight. Although some debate persists regarding some aspects of the genesis of this phenomenon, increased heat loss from the **burn** wound and increased beta adrenergic activity are probably both important factors. Burned skin loses its effectiveness as a barrier to water loss, leading to increased evaporative heat loss via the wound (CALDWELL, BOWSER and CRABTREE, 1981). In addition, radiation heat loss is increased from **burn** wounds (CALDWELL, HAMMELL and DOLAN, 1966), presumably due to high blood flow to the **burn** wound (AULICK *et al.*, 1972). Occlusive dressings can significantly lower the radiation heat loss from **burn** wounds, but evaporative heat loss is not reduced significantly (CALDWELL, BOWSER and CRABTREE, 1981). Consequently, patients with large burns that are treated with occlusive dressings will nonetheless have a high rate of water turnover (GORAN *et al.*, 1990), meaning that fluid and electrolyte requirements are likely to be high to maintain normal urine output and plasma concentrations of electrolytes. Despite persistent increased evaporative loss via the wound, occlusive dressings can greatly minimize heat loss. Also, maintenance of a high room temperature (approximately 90°F) and humidity will further minimize heat loss and thus energy expenditure. Within this context of clinical care, the metabolic response of **burn** patients becomes similar to that of patients with other forms of critical illness.

The role of adrenergic stimulation in causing **burn** hypermetabolism is more controversial than the role of increased heat loss. It has been observed that beta adrenergic blockade can significantly reduce

metabolic rate in patients treated without occlusive dressings (WILMORE *et al.,* 1974), but both acute and chronic beta blockade in burned children treated with excisional therapy and occlusive dressings has not been found to reduce energy expenditure (HERNDON *et al.,* 1988). It therefore seems unlikely that adrenergic blockade can play a significant role in minimizing caloric requirements in patients treated with modern techniques.

2.2. Prediction of resting energy expenditure in burned patients

A large body of data has enabled the development of predictive equations to estimate REE. For example, in a study incorporating 127 observations in 56 burned children, it was found that predicted basal energy expenditure (PBEE) obtained from the Harris-Benedict equation, body surface area and body weight, correlated significantly with REE (CURRERI *et al.,* 1974). On the other hand, neither days post-**burn** nor **burn** size was significantly correlated with REE in that or other studies of patients treated with excisional therapy and occlusive dressings (e.g., GORAN *et al.,* 1991). In an uncomplicated recovery from an injury, one would anticipate a progressive decrease of REE over time until the PBEE is reached. In **burn** injury, this is rarely the case because periods of severe critical illness can occur as much as weeks after injury, thereby disrupting a direct relation between days post-injury and REE. With regard to the lack of relation between **burn** size and REE, it is important to realize that a relation has never been shown to exist at **burn** sizes greater than 40% Even the Brooke Army Base studies, widely referred to as the basis for formulas for caloric requirements (e.g., CURRERI *et al.,* 1974), showed no relationship between **burn** size and REE if smaller burns were excluded from data analysis. Thus, equations predicated on **burn** size overestimate caloric requirements in patients with large burns (WOLFE, 1981). These are precisely the patients least able to tolerate caloric excess.

The single most powerful predictor of REE in **burn** patients is PBEE. In the paper of CURRERI *et al.*,(1974), it was found that in fed patients, on average, REE = 1.29 X PBEE. However, there was considerable variation about this average relation. Only 75% of the predictions were within ± 30% the measured value, and 10% of the measured values varied by more than 45% from the predicted value. Thus, an accurate determination of REE can only be obtained in any given individual patient by direct measurement.

The extensive studies of REE, performed at the Brooke Army Base in the 1970's (e.g., WILMORE *et al.,* 1974), led to the conclusion that REE in adults might be 200-300% greater than predicted basal values. However, these patients were treated neither with early excision of burned tissue nor occlusive dressings. These points are of importance, because studies performed in adults treated with early excision and occlusive dressings have consistently found lower values in adult patients than those reported from the Brooke studies. Although the data base in adults treated with early excision and occlusive dressings is not extensive, the same general observations have been made as in children (GORAN *et al.,* 1991): the PBEE is the most important predictor of REE; **burn** size is not related to REE; the average REE (in the fed state) is about 1.3 times greater than PBEE; and there is a large individual variability between PBEE and REE. In virtually all studies of children and adult patients, REE was lower than 2 X PBEE.

3. Relationship of total energy expenditure (TEE) to REE

Knowledge of the relationship between TEE and REE is essential if REE measurements are to have any value in predicting caloric requirements. This relationship was documented in a recent study in 15 burned children in whom TEE was determined by the doubly-labelled water technique, and REE was determined by indirect calorimetry (GORAN *et al.,* 1990b). TEE was 1.33 ± 0.27 times PBEE and 1.18

± 0.17 times REE in the fed state. Importantly, TEE was significantly correlated with measured REE (r^2 =0.92), but not with PBEE. If the average activity factor, calculated as the difference between TEE and REE, was incorporated into a predictive equation based on the measured value of REE cited above, then it was found that the average energy requirement to maintain energy balance is 1.55 X PBEE. This value is significantly lower than those commonly used for patients with large burns. The caloric intake required to ensure that 95% of patients achieve energy balance is approximately equal to 2 X PBEE. Expressed differently, 2 X PBEE will provide excess caloric intake to all but 5% of patients, and in some patients the excess may be 70% or more above actual requirement. It is therefore reasonable to aim for the average energy intake (1.5 X PBEE), and to adjust that rate either up or down as dictated by tolerance in terms of blood glucose and triglyceride concentrations, as well as body weight changes over time. Although the above data were generated in children, they are very similar to the value for predicted TEE in adults described earlier (GORAN *et al.,* 1991). The need to monitor individual tolerance is particularly important in critically ill patients, who may be intolerant of even maintenance levels of energy intake.

4. Sources of energy

Carbohydrate intake provides nutritional benefit in terms of oxidation as an energy substrate (WOLFE, ALLSOP and BURKE, 1979), some suppression of glyconeogenesis (WOLFE, ALLSOP and BURKE, 1979), and as a consequence of the insulin response suppressing protein breakdown (SHANGRAW *et al.,* 1989) and possibly stimulating synthesis (GORE *et al.,* 1990). On the other hand, a variety of detrimental effects resulting from excess glucose intake, including extreme hyperglycemia, pulmonary overload, and hepatic fat deposition, limit the amount of carbohydrate that can safely be given to critically ill patients. Therefore, some fat should also be given, not only to enable total caloric requirement to be met, but also to prevent essential fatty acid deficiency if nutritional support will be prolonged for weeks. It is reasonable to provide at least 50% of calories as carbohydrate and 20% as fat. In most cases it probably makes little difference whether the remaining 30% of non-protein calories are provided as carbohydrate or fat.

There has been considerable recent activity assessing the optimal form of carbohydrate and fat. Thus, both xylitol and fructose have been proposed as alternative carbohydrates, but little compelling evidence has been obtained supporting an advantage of these compounds over glucose, given that both must first be converted to glucose in the liver before peripheral metabolism is possible. A wide variety of fats have been recently advocated, including fish oil, medium-chain triglycerides, 'structured lipids' in which medium- and long-chain fatty acids are incorporated into the same triglyceride molecule, and triacetin. Future research will be necessary to determine if any of these forms of fat offer distinct advantages over long-chain fatty acids.

5. Protein requirements

Major trauma, burns and sepsis have in common a rapid net **catabolism** of body protein, as well as a redistribution of the nitrogen pool within the body. Muscle protein breakdown is accelerated, whereas certain rapidly produced so-called 'acute-phase' proteins are produced at an increased rate in the liver, wound repair requires amino acids for protein synthesis, and increased immunological activity may also require accelerated protein synthesis. The magnitude of the net **catabolism** of muscle may be so pronounced that maintenance of lean body mass is an unreasonable goal in a critically ill patient. Nonetheless, provision of dietary protein and/or amino acids is essential for minimizing net protein

catabolism. Furthermore, it seems likely that a higher-than-normal intake of protein may be useful. Even the mild stress of simple bed-rest increases the protein requirement to maintain N balance (STUART *et al.,* 1988). However, it is also clear that there is a limit to the extent to which increased protein intake can ameliorate net protein **catabolism** in a previously well-nourished critically ill patient. Protein intake greater that 1.5 g protein/kg/d has not been shown to provide any advantage (e.g., WOLFE *et al.,* 1983) and can result in increased concentrations of urea and ammonia. Consequently, it is recommended that protein be provided to adults at a rate between 1.2 and 1.5 g protein/kg/d. Data quantifying protein requirements in children are lacking. However, since they would normally require more protein than adults in order to support growth, it is reasonable to assume that a higher protein intake might be useful. Thus, it is not uncommon to give as much as 3 g protein/kg/d to burned pediatric patients. Nonetheless, at this time there is no compelling evidence that there is any advantage to providing more than 2 g protein/kg/d. Protein containing a well-balanced mixture of amino acids would seem to be the most advantageous for both adults and children. Formulations enriched with branched-chain amino acids have been promoted, but clinical trials have failed to show a clinical advantage in most critically ill patients, particularly when concentrations of other amino acids in the unbalanced formulation be come rate-limiting for protein synthesis. More recently, research has focused on the importance of glutamine intake in critically ill patients. Since both oral and enteral formulations have omitted glutamine entirely, it is not surprising that some beneficial effects have been found with the addition of glutamine, particularly in terms of improving N balance (which may reflect repletion of the free intracellular glutamine pools). However, it is not yet clear if there is any advantage in terms of protein synthesis to adding glutamine in an amount in excess of its normal contribution to protein composition. Other specific amino acids, such as arginine and histidine, have also been promoted as having specific, unique 'pharmacologic' effects, but convincing experimental evidence in humans supporting these claims is not yet available.

Acknowledgements

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REVIEW ARTICLE

Current Treatment of Severely Burned Patients

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Objective The authors provide an update on a multidisciplinary approach to the treatment of severely burned patients. A review of studies and clinical trials from the past to the present include fluid resuscitation, sepsis, immune function, hypermetabolism, early excision, wound healing, scar formation, and inhalation injury.

Summary Background Data Advances in treating initial burn shock, infection control, early wound closure, and modulation of the hypermetabolic response have decreased morbidity and mortality in the last two decades. Specialized burn care centers, using a multidisciplinary approach, not only successfully treat large burns and their complications, but provide the necessary rehabilitation and psychological support required for readjustment back into society.

Conclusions Thermal injury results in a number of physiologic alterations that can be minimized by adequate fluid resuscitation to maintain tissue perfusion, early excision of burn wounds, and rapid wound coverage. These measures, in combination with antibiotic coverage and nutritional support in the form of early enteral tube feedings, will decrease the hypermetabolic response and the incidence of sepsis that can lead to hemodynamic instability and organ failure. Ongoing clinical trials using anabolic agents (*e.g.*, recombinant human growth hormone) and pharmacologic agents that modulate inflammatory and endocrine mediators (*e.g.*, ibuprofen and

propranolol) show promise in the treatment of severe burn injuries.

Major **burns** are relatively common injuries that require multidisciplinary treatment for patient survival and recovery. More than 1 million **burn** injuries occur annually in the United States. Although most of these **burn** injuries are minor, 60,000 to 80,000 people require admission to a hospital or to a major **burn** center for treatment, and 5000 of these patients die each year. In recent years, advances in **burn** treatment have reduced mortality rates and have improved the quality of life for **burn** survivors. Improvements have been made in treating initial **burn** shock, providing appropriate resuscitation, controlling infections, and performing life-saving and scar-reducing surgical interventions. Team efforts by surgeons, nurses, scientists, and a vast array of therapists are making productive and social lives possible for many **burn** victims.

Thermal injury is associated with anatomic, physiologic, endocrinologic, and immunologic alterations, which require specialized care. Cutaneous injury results

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in significant fluid loss as well as the release of multiple inflammatory mediators. When disseminated by the circulation to central organs, bacteria and inflammatory mediators can cause cardiovascular compromise, a breakdown of gastrointestinal mucosal integrity, and, ultimately, multiple organ failure. Inhalation injury can further accelerate these responses. Specialized **burn** care centers and research institutions emphasize a multidisciplinary team approach that strives to preserve organ function while promoting rapid wound closure and eventual rehabilitation.

The success of recently adopted team approaches in **burn** treatment is evidenced by improved survival and rehabilitation over the past 40 years. Before 1950, a pediatric patient with a 50% total body surface area (TBSA) **burn** injury had about a 50:50 chance of survival. [1] In the early 1990s, an equivalent mortality rate was seen only in children who had more extensive injuries, in excess of 95% TBSA **burns**. [2] With increases in survival, functional, physical, and psychological rehabilitation have come to the forefront as the new challenges facing clinical team members treating **burn** patients.

Advances in medical care have changed the principal cause of death in **burn** patients from **burn** shock to wound sepsis. In the 1940s and 1950s, inadequate fluid resuscitation during the immediate hours after a **burn** injury resulted in 20% to 40% of deaths among **burn** patients. With the advent of vigorous fluid resuscitation in the 1960s and 1970s, irreversible **burn** shock has been replaced by wound sepsis as the leading cause of death in the **burn** population. The development of topical and systemic antimicrobial agents, advances in nutritional support for the hypermetabolic response, and the use of surgical techniques for early **burn** wound excision have now changed the primary cause of death from wound sepsis to pulmonary sepsis, which often follows an inhalation injury. [3] [4] [5] [6] Overall, advances in the treatment of initial injuries and their complications as well as new surgical techniques for closing wounds and reducing scar tissue have increased **burn** patients' chances not only of survival but also of recovery and readjustment into society.

BURN SHOCK, RESUSCITATIVE REGIMENS, AND INFLAMMATORY MEDIATORS

Burn shock is characterized by a combination of hemodynamic and local tissue alterations. Hemodynamic changes that occur after a severe thermal injury include decreased cardiac output and decreased extracellular and circulating plasma volumes, all of which contribute to hypovolemic shock.

Inflammatory mediators (including cytokines, prostaglandins, nitric oxide, and superoxide ions) have been implicated in causing additional tissue damage. It is postulated that, although locally beneficial, such mediators induce undesirable effects when they reach high levels. For example, further tissue injury may occur because of the release of proteolytic enzymes and superoxide ions from activated macrophages and leukocytes. [7] Interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha have been shown to be potent chemical messengers that can induce immunologic depression and **catabolism** during the initial weeks following a **burn** injury. [7] [8] In a recent study, IL-1beta and IL-6 were detected more frequently in the plasma of **burn** patients than in the plasma of control subjects. In addition, the levels of IL-6 were significantly higher in patients who died of their **burn** injuries compared with those of patients who survived. [8] (Fig. 1) .

Arachidonic Acid Metabolites

Prostaglandins and leukotrienes are vasoactive products of arachidonic acid metabolism. Macrophages, neutrophils, platelets, and endothelial cells release these substances at the **burn** site and contribute to the hemodynamic inflammatory response. Prostaglandin E2 causes postburn vasodilation and the accumulation of neutrophils at the **burn** site. [9] [10] [11] The prostaglandins and leukotrienes B4 to D4 increase microvascular permeability.

Thromboxane A2 (TXA2) and B2 (TXB2), along with their metabolites, are produced locally in a **burn** wound and are released from circulating platelets. The thromboxanes cause tissue damage within the **burn** wound. It has been shown that the release of TXB2 at the **burn** wound site is associated with local tissue ischemia and that thromboxane inhibitors can reduce this dermal ischemia. [12] [13] [14] [15] [16] [17] [18] [19] [20] The TXA2 synthesis inhibitor anisodamine has been shown to be beneficial in such cases by attenuating hemodynamic and rheologic disturbances. [18] In addition, Demling and LaLonde showed that topically applied prostaglandin antagonists decrease local prostanoid production in **burn** tissue and, subsequently, decrease wound edema without altering systemic prostaglandin production. [19] In addition, animal studies have shown that systematically administered ibuprofen attenuates the characteristic postburn pulmonary artery vasoconstriction that reduces oxygen delivery and mesenteric vasoconstriction that may contribute to bacterial translocation [20] (Fig. 2) .

Resuscitative Regimens

Retrospective analysis of the fluid requirements for **burn** patients has led to the development of fluid regimens that are based on **burn** size. [21] [22] [23] [24] The development and worldwide propagation of standard methods for assessing

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Figure 1. Schematic summary of some of the pathophysiologic changes that occur after a severe thermal injury. The wound releases mediators (cytokines, prostaglandins, and thromboxanes) that contribute to a hypermetabolic state and changes in vascular permeability. Thromboxanes induce vasoconstriction locally and systemically, affecting vascular beds and therefore perfusion to the gut and kidneys. Locally thromboxanes reduce perfusion to the wound causing ischemia and promoting susceptibility to wound infection. Inhalation injury combined with **burn** shock and translocated toxins contributes to multisystem organ failure. The ensuing chemical maelstrom may progress to multisystem organ failure and death.

burn size, such as the rule of nines and the Lund and Browder charts, has aided in the application of these formulas. Severe systemic edema continues to be a major complication following **burn** injury. Although attempts have been made to limit edema formation by modifying the resuscitative regimen, no

single fluid resuscitation formula has proven to be superior. The recommended fluid compositions and formulas proposed primarily were derived on the basis of retrospective patient studies. The Parkland formula advocates the use of Lactated Ringer's solution alone and estimates the fluid requirement for the first 24 hours after **burn** injury to be 4 mL/kg/% TBSA **burned** (Table 1) , whereas the Brooke formula recommends 2 mL of Ringer's lactate/kg/% TBSA **burned** plus 2000 mL of 5% dextrose solution during the first 24 hours postburn. The formula used at the Shriners **Burns** Institute in Galveston, Texas, is composed of lactated Ringer's solution containing 1.25% salt-poor human albumin; it is more appropriate for pediatric patients because of their greater ratio of surface area to volume. [23] According to this formula, fluid requirement during the first 24 hours is 5000 mL of Ringer's lactate/m^2 **burned** and then 2000 mL/m^2 TBSA for maintenance during the first 24 hours postburn. Fifty percent of the calculated fluid volume in each of these formulas is administered during the first 8 hours after **burn** injury, and the remaining 50% is administered over the next 16 hours (Table 1) . These formulas differ only in the quantity of colloid given. In general, the use of colloid reduces the total fluid volume requirement. Considerable research has focused on the issue of when to and whether to use colloid-containing fluids. The consensus is that the administration of colloid is unnecessary for patients with **burns** of less than 40% TBSA and during the first 8 hours for patients with large **burns** because it does not reduce fluid loss into surrounding tissues, which occurs with these larger injuries. The generalized increase in capillary permeability that occurs with large **burns** results in the loss of albumin as well as other plasma proteins from the circulation. This problem is compounded by a reduction

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Figure 2. Summary of techniques to enhance wound healing and reduce detrimental sequelae of hypermetabolism. Growth hormone enhances donor site wound healing. Early excision helps to reduce the source of mediators that perpetuate the hypermetabolic response. Beta blockers reduce the affects of excessive catecholamines, in particular, reducing heart rate and cardiac work. Topical antiprostaglandins decrease local prostanoid production in the wound, which decreases wound edema. Systemic antiprostaglandins can attenuate detrimental vasoconstriction in the mesenteric and pulmonary vascular beds. Nebulized agents reduce cast formation, atelectasis, and, therefore, susceptibility to pulmonary infection. Rapid early fluid resuscitation helps to maintain systemic blood pressure and therefore profusion to essential regions, such as the kidneys and gastrointestinal tract. This helps to reduce such complications as acute renal failure and bacterial translocation from the gastrointestinal tract. Antibacterial agents help to reduce **burn** wound infection and systemic sepsis. In combination, these techniques reduce morbidity and mortality rates.

in hepatic albumin synthesis, which is a classic feature of the acute-phase response. Colloid administration after acute resuscitation with human albumin or with plasma protein substitutes helps in maintaining oncotic pressure, but in randomized studies, it has not been shown to result in any improvement in the clinical outcome.

A hypertonic formula involves a resuscitation fluid

TABLE 1 -- TYPICAL FLUID VOLUME ESTIMATES FOR A 150-LB MAN WITH 40% TBSA **BURN** DURING THE FIRST 24 HOURS POSTBURN

	Evans Formula *	Brooke Formula	Parkland Formula
Colloid	1.0 mL/kg/%	0.5 mL/kg/%	
	(2800 mL)	(1400 mL)	None
Crystalloid	1.0 mL/kg/%	1.5 mL/kg/%	4.0 mL/kg/%
	(2800 mL)	(4200 mL)	(11,200 mL)
Free water	2000 mL	2000 mL	None

* 24-hr total = 7000 mL; 48-hr total = 12,400 mL; urine 30-50 mL/hr.

24-hr total = 7000 mL; 48-hr total = 12,400 mL; urine 30-50 mL/hr.

24-hr total = 11,200 mL; 48-hr total = 14,000 mL; urine 30-50 mL/hr.

containing 250 mEq of sodium balanced with lactate and chloride; it is administered at a rate of 2 mL/kg/hour and adjusted to maintain a urine output of 1 mL/kg/hour. [21] [22] [23] [24] Theoretically, less overall fluid can be administered with this technique to high-risk patients; however, there continues to be a heated debate over the safety of this technique. Although fluid formulas are beneficial for the maintenance of cardiac output and blood pressure, reversing the vasoconstrictive effects of thromboxanes and other mediators, particularly in such areas as the gut, remains unsolved. Potential areas for future research in this area include the development of fluids and pharmacologic agents designed to improve perfusion to specific vascular beds, such as the gut and kidneys, without overloading others, such as the lungs and wounds.

SEPSIS

Sepsis is the major cause of death among **burn** patients, although its cause and incidence have changed over the past 20 years. Streptococcal and pseudomonal **burn** wound infections were once the main causes of sepsis and death; however, because of early wound excision, topical antimicrobials, and improved wound dressings,

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the incidence of such infections has decreased significantly. Despite improvements in fluid resuscitation and the maintenance of adequate cardiac output and renal perfusion, **burn** victims still have a clinically significant reduction in intestinal blood flow. The reduced perfusion and subsequently reduced oxygenation in the gut leads to a breakdown in mucosal integrity and allows bacteria and their toxins to pass through this barrier. Peak endotoxin concentrations have been observed as early as 12 hours after injury. Many bacteria are trapped in the lymph nodes, but some become disseminated systematically, where they seed other tissues. [25]

Results of animal studies suggest that gut blood flow may be open to pharmacologic manipulation. The production of vasoconstrictors, by local release of thromboxane and systemic vasopressin have been shown to parallel the postinjury rise in mesenteric vascular resistance. The maintenance of gut perfusion

through the use of vasodilators, such as nitroprusside, and the blockade of key enzymes, such as thromboxane synthetase, required for the synthesis of vasoconstrictors like thromboxane, have been shown to reduce bacterial translocation. [26] [27] [28] Further, the use of early enteral feeding improves mucosal blood flow reduce mucosal atrophy and subsequent translocation.

The development of topical antimicrobial agents, such as silver sulfadiazine, mafenide acetate, and silver nitrate, the use of perioperative systemic antibiotics and wound surveillance techniques, such as wound biopsy and blood culture, has lead to a decrease in mortality rates due to wound sepsis. [29] [30] [31] [32] [33] [34] [35] [36] [37] [38] [39] In addition, there has been a shift in the initial observance of wound sepsis during a clinical course. During the 1960s, **burn** wound sepsis manifested much earlier than it does today. This change is attributed to better nursing care in general and to antimicrobial management in particular. The general use of oral and topical antifungal agents has been shown to decrease candidal infection. [32] [33] The regular use of wound biopsies as well as tissue and blood cultures has allowed for the more specific and controlled use of systemic antimicrobial agents. [34] [35] [36] [37] [38] [39] [40] Unfortunately, the increased use of broad-spectrum antimicrobials has led to the emergence of multiresistant microbes, such as multiresistant *Staphylococcus aureus*, and resistant strains of *Pseudomonas* and enterococci.

IMMUNE FUNCTION

After thermal injury, a systemic down-regulation of immunologic activities occurs. This shift is characterized by a reduction in the number of lymphocyte subpopulations, reduced macrophage and neutrophil phagocytic killing ability, and decreased levels of opsonins, immunoglobulins, protease inhibitors, and chemotactic factors. [41] [42] [43] [44] The expression of neutrophil receptors and the binding properties of intracellular adhesion molecules are altered to allow for neutrophil migration. [45] [46] [47] [48] Warden et al. demonstrated that leukocyte chemotaxis is inversely correlated with clinical status and is a predictor of survival. [49] [50] Similar changes have been noted in monocytes recovered from the plasma of **burn** patients. It is noteworthy that several commonly used topical and systemic chemotherapeutic agents suppress leukocyte chemotaxis and, therefore, are used sparingly or in rotation with less toxic agents. [36] [38] Other deleterious effects of thermal injury on the immune system include a reduction in lysosomal enzyme levels (beta glucuronidase, lysozyme, and myeloperoxidase) and reduced production of hydrogen peroxide and superoxide. [51] [52] [53] [54] [55] Neutrophils harvested from **burn** patients show significantly depressed oxygen consumption compared with cells harvested from control subjects without **burns**. [56] Trials using immune function stimulants, such as isoprinosin, IL-2, and IL-5, are underway. [57]

HYPERMETABOLISM

Studies performed by Cuthbertson in 1932 indicated that the period immediately following trauma is associated with relative or absolute anuria of varying duration. This early phase, or ebb phase, is followed by a more prolonged flow phase, which is associated with increased urinary output, nitrogen loss, increased oxygen consumption, and elevated body temperature, which can rise as high as 38.5 C. [58] **Burn** patients manifest a particularly severe and prolonged "flow" or "hypermetabolic" phase that lasts several weeks and is associated with massive protein **catabolism** and lipolysis. This phase can result in peripheral muscle wasting and hepatic fat deposition.

The metabolic rate of **burn** patients typically is elevated because of fluid and heat loss. Thermally injured skin has been shown to be considerably more permeable to fluid than is an intact integument, and evaporative water loss of approximately 4000 mL/m^2 TBSA **burned** has contributed to the extensive fluid requirements of **burn** patients. More than 30 years ago, it was postulated that evaporative heat loss stimulated a compensatory rise in metabolic rate. [59] Animal studies supported this view. [60] [61]

Investigators found that rats subjected to a 5% to 20% TBSA full-thickness **burn** had elevated extrarenal water loss accompanied by increased oxygen consumption and metabolic rate. Further, water loss and metabolic rate decreased when the wound was covered by an impermeable dressing. [59] [60] [61] A separate study measured water loss and metabolic rates in thermally injured rats at three environmental temperatures: 24 C., 28 C., and 32 C. [61] The results indicated that for a given **burn** size, the metabolic rate was less at 32 C. than at lower temperatures.

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The authors suggested that because the environmental temperature was equal to that of the wound, less energy was required to replace body heat lost to evaporation. [61] The authors suggested that the combination of an occlusive dressing and a sufficiently high environmental temperature could significantly ameliorate the hypermetabolic response. [60] [61] [62] [63] Closure of the **burn** wound by natural contraction or by such treatment as grafting reduced water loss and hypermetabolism; however, clinical studies involving early wound excision revealed that early wound coverage alone cannot attenuate the hypermetabolic response to large **burns**. [64]

The hormonal manifestations of hypermetabolism include increased cortisol, catecholamine, and glucagon, which increase glucose flow proteolysis, lipolysis, and gluconeogenesis. [65] [66] The **burn** wound itself contributes to the hypermetabolic state by releasing inflammatory mediators and cytokines. [67] [68] The increased glucose pool created by the catabolic state is the body's attempt to provide fuel for reparative processes. Studies indicate that the provision of early enteral feeding helps to decrease weight loss as well as gut atrophy, bacterial translocation, and subsequent sepsis. In many centers, enteral feeding is introduced within 4 hours of commencing fluid resuscitation. In fact, liquid feeding may, in many cases, totally replace intravenous resuscitation. Several formulas have been devised to maintain weight in adults and children. [69] [70] [71] These formulas do not preserve normal body composition; peripheral protein and fat wasting proceed with central fat deposition in the liver and bowel mesentery. A series of reports by Wilmore and coworkers associated the hypermetabolic response with elevated blood levels of catecholamines. The authors were able to mimic the postburn hypermetabolic response in healthy volunteers by continuously infusing a combination of cortisol, glucagon, and epinephrine. [67] [68] The hypermetabolic state can lead to excessive catecholamine secretion, which can cause cardiomyopathy, focal necrosis, and myocarditis. [72] [73]

Over the past 30 years, multiple studies have confirmed the usefulness of growth hormone in reducing or reversing the negative nitrogen balance associated with severe stress. [74] [75] [76] [77] [78] Growth hormone is an anabolic peptide hormone liberated from the pituitary gland in response to stress, hypoglycemia, exercise, and elevated plasma amino acid levels. The use of exogenous growth hormone, however, may precipitate or exacerbate hyperglycemia and insulin resistance. [79] It has been demonstrated recently that insulin-like growth factor-1 (IGF-1) administration can attenuate the hypermetabolic response to thermal injury as well. [80] Animals treated with IGF-1 maintain body weight to a significantly greater extent than animals receiving only a placebo. The mechanism by which IGF-1 concomitantly decreases metabolic rate and increases whole-body anabolic activity remains unclear; however, these effects warrant further investigations. Although IGF-1 is thought to mediate some of the effects of growth hormone, investigations involving healthy volunteers indicate that a combination of IGF-1 and growth hormone would be advantageous in eliciting greater protein anabolism and lower plasma amino acid levels than either substance alone. [81] Unfortunately, the administration of exogenous growth hormone can precipitate or exacerbate hyperglycemia, a problem requiring therapeutic insulin administration. The combination of growth hormone and IGF-1 or insulin is clinically attractive in that it would decrease the incidence of hypoglycemia and hyperglycemia and potentiates the metabolic benefits (Fig. 2) .

The nonselective beta-adrenergic blocker propranolol has been used successfully to reduce heart rate and cardiac work; however, a side effect of this treatment is lipolysis blockade. [82] Recently, the chronic administration of the selective $beta_1$ -adrenergic receptor blocking agent metoprolol to patients with large thermal injuries has been shown to decrease heart rate and myocardial work without adversely affecting lipid kinetics. [83] Animal studies of $beta_2$ -adrenergic agonists, such as salbutamol and clenbuterol, have exhibited reduced proteolysis and stimulated anabolism. [84] Further research is needed to effectively counteract the hypermetabolic response to **burn** injury.

EXCISION THERAPY

Methods for handling **burn** wounds have changed in recent decades. Traditional **burn** wound management involved applying topical antibiotics in dressings, changed twice daily until the eschar separated (an interval requiring 3 to 5 weeks of waiting) and applying topical antibiotics. Separation occurred by liquefication of necrotic **burn** tissue by proteolytic enzymes released from proliferating pathogens within the wound. Pseudomonal and beta-hemolytic streptococci were the main culprits. Twenty years ago, Janzekovic, in her review of 2615 patients, demonstrated that early removal of the **burn** tissue by tangential excision reduced pain, number of operative procedures, and length of hospital stay. [85] In addition, patients achieved better functional and aesthetic results than could be achieved with more conservative techniques of excision and grafting. Early excision also reduced mortality rate [86] [87] [88] and blood loss because the original tissue was removed before the characteristically vascular granulation tissue had formed. Desai et al. showed that patients who underwent excision for wounds more than 2 days old lost twice as much blood as patients receiving identical surgery 24 hours earlier (0.8 mL/cm^2 /TBSA **burn** *vs.* 0.4 mL/cm^2). [88] Early excision

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is especially appropriate for flame and dry heat injuries, whereas a more conservative approach is indicated for scald injuries which are often associated with less severe second-degree **burns** that are likely to heal well without excessive scarring. [89] The results of a prospective randomized study in a pediatric population showed that scalded patients should be observed for approximately 14 days, after which the need for operative intervention can be reassessed. [89]

Massive **burns** (>60% TBSA) present the surgeon with the difficulty of locating adequate donor sites. This problem is circumvented with the use of widely expanded, meshed (4:1), autologous split-thickness grafts that can be overlaid with unexpanded, meshed, homologous (cadaver) split skin. [90] This technique is particularly applicable in areas where cosmesis is less important. [90] Rapid epithelialization of the interstices between the meshed autograft achieves wound closure. The re-epithelialized wound allows the overlaid homografts to be shed before an acute rejection occurs. In the future, cultured allograft epidermal cells may be used as a replacement for cadaver skin. Cultured skin would be pathogen free and more universally available than cadaver skin and might also produce growth factors that would enhance the would healing process.

WOUND HEALING

Wound healing involves a complex process of cellular interactions coordinated by the paracrine and autocrine activity of cytokines and growth factors. Genetically engineered recombinant substances are now available for use in the modulation of wound healing. Wound growth factors can be grouped into three categories corresponding to their functions: mitogens, chemoattractants, and transforming factors (the latter affect cellular phenotype). [91] The most promising growth factors include epidermal growth

factor, fibroblastic growth factor, platelet-derived growth factor, and transforming growth factor-alpha. Receptors for these factors are expressed by many cells found in a wound. Accelerated wound healing has been demonstrated in skin graft donors treated with a combination of topical silver sulfadiazine and epidermal growth factor as opposed to topical silver sulfadiazine alone. [92] Although useful individually, the combination of these topical agents is likely to produce optimal results.

Growth hormone influences collagen and, therefore, skin texture. Patients with acromegaly have tough, thick skin, whereas patients deficient in growth hormone have much more delicate skin. [79] [93] Animal studies have confirmed the efficacy of growth hormone on collagen deposition, wound healing, and subsequent tensile strength. [94] [95] [96] A recent study from Shriners **Burn** Institute in Galveston confirmed the results of previous studies and demonstrated the clinical effectiveness of two forms of recombinant human growth hormone in reducing donor site healing times. [97] [98] Children with greater than 40% TBSA **burn** with a 20% or greater TBSA full-thickness **burn** received either a growth hormone or a placebo (saline) through subcutaneous or intramuscular injection. The results showed a reduction in healing time from 8.5 ± 2.3 days for the placebo to 6.8 ± 1.5 and 6.01 ± 1.1 days respectively for two forms of recombinant growth hormone used in the study. [98] In addition, the length of hospital stay (used as an indicator of clinical benefit) was reduced by an estimated 25% for groups receiving recombinant growth hormone. [98] [99] Additional beneficial effects included increased muscle strength and a feeling of well-being. [99] Recombinant human growth hormone therapy has also been demonstrated to be economically advantageous by reducing overall hospital costs by as much as 23%. [100]

In massive thermal injuries in which autologous donor skin is limited, wound closure must be achieved through alternative techniques. Major advances have been made in the area of wound dressings and skin substitutes. Allogenic skin is the most commonly used substitute; however, studies are underway to develop alternative materials that would provide wound closure. Three substitute materials whose makeup is based on matrix structure and cellular content are under development. The first uses a noncellular matrix material to mimic the three-dimensional structure and character of dermis along with a silastic covering membrane to mimic the physical properties of the epidermis. The second uses an epidermal cell culture technique intended to replace the epidermis alone. The third uses a combination of matrix and cell culture techniques to create a composite graft material. The only reported prospective and controlled clinical study [101] that has involved the use of permanent wound closure materials used the artificial dermis (Integra) designed by Yannas and Burke. [102] [103] [104] [105] The conclusion of this multicenter trial was that Integra provided a wound cover that produced results at least as satisfactory as currently available skin grafting techniques and that it allowed for the use of thinner grafts, resulting in the more rapid healing of donor sites.

Initially cultured epidermal autografts produced very encouraging results, particularly in patients with major thermal injuries greater than 90% TBSA **burn**. Unfortunately, because of exorbitant costs, high failure rates, copious scar formation, and tenuous skin coverage, optimism for this technique has declined. The most promising approach under study may be the use of artificial skin, which consists of allodermis or collagen mesh sealed with a sheet of synthetic material which could be used in any environment. The material could be impregnated

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with autologous epithelial cells at a later date and grown to resemble the original bilaminar skin. [102] [103] [104] [105] [106] The use of cultured autologous tissue for **burn** wound closure has remained in an early stage of development and application. [107] We hope that with continuing research, this area will lead to more cost-effective and refined methods for treating patients with life-threatening thermal injuries.

SCAR FORMATION

Long-term follow-up of pediatric patients with severe thermal injuries has demonstrated significant alteration in the psychosocial development of adolescents, which may be attributed partially to appearance. Prioritization and systematic planning of the reconstructive needs of these patients may alleviate some disfigurement and improve function but will not eliminate scarring. Full-thickness grafts and moist environment healing show promise for cosmetic enhancement.

The long-held belief that wounds heal best in a moist environment has been confirmed by multiple investigators. A recent prospective study in which skin-grafted bilateral tattoo excisions were covered with an occlusive membrane, or dry gauze showed that skin grafts assessed 1 year later were softer and more durable in wounds kept moist with their own fluid for only 1 week compared with those allowed to dry. [108] Full-thickness skin grafts provide the greatest level of function to a healed wound. In a recent skin graft study in a rat model, full-thickness skin grafts exhibited earlier, more homogenous, and greater levels of sensory function than split-thickness skin grafts. [109] Other advantages of full-thickness skin grafts include less tendency for contracture and better cosmesis.

Burns that involve the reticular dermis are believed to be more prone to unsightly hypertrophic scarring. Deitch et al. [110] observed a 33% incidence of hypertrophic scarring in wounds that healed between 14 to 21 days and a 78% incidence in **burns** taking more than 21 days to heal. Furthermore, any factor that delays the healing process can predispose a wound to hypertrophic scarring. Wound depth, time of healing, infection, genetic predisposition, and immunologic factors have all been implicated in hypertrophic scarring; however, the precise pathophysiologic process and mechanisms responsible for this phenomenon have not been identified. Although the first reference to compression therapy for hypertrophic scars is attributed to Ambroise Pare in the 16th century, acceptance of the concepts of pressure, positioning, and splinting in the management of hypertrophic scars did not gain widespread acceptance until Larson et al. [111] published their results from Shriners **Burns** Institute in Galveston in the 1970s. Although the use of pressure to treat hypertrophic scarring is now almost universal, it is important to note that no study validates the mechanisms by which it works, nor have controlled clinical trials been conducted. In general, all methods are more effective when prophylactic treatment is commenced before wound hypertrophy occurs. Several preventive methods are in use, including the application of elastic wraps, which are effective, inexpensive, and can be applied early. Tubular compression bandages are also effective and inexpensive modes of pressure treatment. Custom-fit garments are more appropriate for the maintenance of long-term pressure once wound closure is achieved, but this form of treatment is expensive.

INHALATION INJURY

Smoke inhalation injury is a major cause of death in **burn** patients. The pathophysiology of inhalation injury is complex and not fully understood. The inhalation of smoke appears to trigger the release of the vasoconstrictor thromboxane, which causes an increase in pulmonary artery pressure formation. [112] The chemicals in smoke also cause direct damage to the respiratory epithelium, leading to the chemotatic attraction of neutrophils and subsequent release of proteolytic enzymes. Tracheobronchial injury results in sloughing of the respiratory tract mucosa and impairment of the normal mucociliary clearance mechanism. Sloughing of the mucosa results in cast formation, aggregates of mucus, and cellular debris, which obstruct moderate-sized airways, and these complications lead to distal atelectasis, air trapping, and increased barotrauma. Disruption of endothelial and epithelial integrity results in exudation of protein-rich plasma into terminal airways, which, in combination with atelectasis, leads to bacterial growth and the subsequent development of pneumonia. Injury to Type II pneumocytes impairs surfactant

production, and contributes to the pathologic process. [113] [114] [115]

Treatment for patients with severe inhalation injury involves supportive care with conventional volume-cycled positive-pressure ventilators, supplemental oxygen, and intensive tracheobronchial toilet. The use of prophylactic antibiotics has not altered the mortality rate associated with severe inhalation injury. High-frequency ventilation may be beneficial in the clearance of secretions, thereby recruiting and stabilizing collapsed and diseased lung segments. [116] [117] [118] [119] An increased survival rate and a decreased incidence of pneumonia have been demonstrated in patients treated prophylactically with high-frequency ventilation. These observations suggest that high-frequency ventilation may benefit patients with inhalation injury by maintaining the patency of distal airways, thereby improving the clearance of secretions.

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The long-held belief that fluid resuscitation should be limited in the event of a combined **burn** and inhalation injury has not been supported by a recent prospective trial. [120] [121] In fact, patients with both injuries required more fluid during the first 24 hours postburn (measuring 2 mL/kg/TBSA **burned**) than patients with **burn** injuries alone. The additional volume did not lead to pulmonary edema. Separate trials using thromboxane inhibitors and agents preventing the release of proteolytic enzymes have been shown to decrease lung water accumulation following inhalation injury. Free-radical scavenging agents, such as dimethylsulfoxide or n-acetyl-cysteine, can be given as aerosols and can decrease lung fluid formation. In addition, the nebulized combination of a free-radical scavenging agent, such as n-acetyl-cysteine, with heparin improves lung function by decreasing cast formation, small airway obstruction, and barotrauma. [121] [122] Agents used to treat alpha$_1$ -antitrypsin deficiency may also prove to be beneficial in the treatment of pulmonary injury.

SUMMARY

Burn injuries alter a number of physiologic functions that place a patient at risk for serious complications. The adequate and rapid institution of fluid resuscitation maintains tissue perfusion and prevents organ system failure. Sepsis is controlled by early excision of **burn** wounds and topical antimicrobial agents. Patients who have sustained an inhalation injury require additional fluid resuscitation, humidified oxygen, and, occasionally, ventilatory support. Enteral tube feeding is commenced early to control stress ulceration, maintain intestinal mucosal integrity, and provide fuel for the resulting hypermetabolic state. Centralized care in **burn** units has promoted a concentrated team approach that has promoted clinical studies to examine such issues as fluid resuscitation, nutrition, wound excision, and temporary wound coverage. Further studies are required to address the primary determinants of death, inhalation injury complications, and pneumonia as well as to ameliorate pain and scar formation, which are the persistent sequelae of this thermal injury. Through the use of aggressive resuscitation, nutritional support, infection control, surgical therapy, and early rehabilitation, better psychological and physical results can be achieved for **burn** patients.

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